Amendments to the Specification

Please amend the specification in the indicated paragraphs as provided below.

[0006] Met, the protein product of the c-met-protooncogene, was discovered and studied in the laboratory of George Vande Woude at the National Cancer Institute beginning in 1984 (Cooper C S et al., 1984, Nature 311:29-33; Dean M et al., 1985, Nature 318:385-388; Iyer A et al., 1990, Cell Growth Differ 1:87-95) Met is a receptor protein tyrosine kinase of the same family as epidermal growth factor (EGF) receptors. This transmembrane protein acts as the cell surface membrane receptor in which the extracellular domain (ECD) binds hepatocyte growth factor/scatter factor (HGF/SF, also abbreviated HGF herein). The amino acid sequence for Met, HGF, and the ECD of Met are shown in the Sequence Listing as SEQ ID NOs 1-3, respectively. The cDNA sequences for Met and HGF are shown in the Sequence Listing as SEQ ID NOs 4 and 5, respectively. Met dimerizes after binding ligand to form the active kinase. The intracellular tyrosine kinase domain activates a complex cascade of biochemical reactions. Under normal conditions Met is a keystone molecule, acting on the molecular signaling pathways responsible for cellular differentiation, motility, proliferation, organogenesis, angiogenesis, and apoptosis (Haddad R et al., 2001, Anticancer Res 21:4243-4252). In neoplastic cells the aberrant expression of Met and HGF leads to emergence of an invasive/metastatic phenotype. Supporting this are results of transfection experiments and retrospective analyses of many types of human solid tumors, including cancers originating in the head and neck, thyroid, lung, breast, stomach, liver, pancreas, colon and rectum, kidney, urinary bladder, prostate, ovary, uterus, skin, bone, muscle, and other connective tissues [Haddad et al., supra; (Stuart, K A et al (2000) Int J Exp Path 81:17-30; van der Voort, R et al. (2000) Adv Cancer Res 79:39-90). Both paracrine and autocrine mechanisms of Met activation by HGF occur in human neoplasms. Moreover, activating mutations in Met--either inherited in the germ

line or found in sporadic cancers--have been shown to contribute to a variety of human cancers (Schmidt L et al., 1997, Nat Genet 16:68-7313).

[0023] Silvagno et al., Arterioscler Thromb Vasc Biol 15:1857-1865 (1995) described using a Met agonist antibody in vivo to promote angiogenesis in MATRIGELMatrigel® plugs.

[0029] Many different radiopharmaceuticals are available for imaging neoplasms. They range from classical agents such as sodium iodide (Na-^{131}I, thallium chloride (^{201}TlCl), and gallium citrate (^{67}Ga-citrate) to highly selective positron-emitting reporter gene detection systems (Vallabhajosula S (2001), In: Nuclear Oncology. I Khalkhali et al., eds. Lippincott Williams & Wilkins, Philadelphia, Pa. pp. 31-62; Iyer M et al. (2001) J Nucl Med 42, 96-105). Radiolabeled molecules that bind to specific cell surface components provide one successful approach to tumor imaging and therapy. Examples are OCTREOSCANOctreoScan® for imaging and potentially treating neuroendocrine neoplasms, CEASCANCEAScan® and ONCOSCINTOncoScint® for imaging colorectal and ovarian cancers, and BEXXARBexxar® and ZEVALINZevalin® for detecting and treating certain lymphomas.

[0115] The mAbs and combinations of the present invention, along with various names used for each mAb (some being abbreviations of longer designations) are shown in Table 1, below. The hybridomas producing these mAbs have been were deposited in the American Type Culture Collection (ATCC), 10801 University Blvd., Manassas, VA, 20110-2209, USA, on the following dates: mAb Met3 on May, 14, 2002; mAb Met5 on June 21, 2002; and mAbs HGF (A.1, A.5, A.7, and A.10) on May 30, 2001prior to the filing of the present application. Their ATCC Patent Deposit Designations (or accession numbers), are provided in Table 1.

[0119] Anti-hMet mAbs alone, preferably Met3 or Met5, a combination of anti-hMet mAbs, e.g., Met3+Met5, or a combination of one or more anti-hMet mAbs with anti-hHGF mAbs, offer a

novel approach in the imaging by, for example, radioimmunoscintigraphy (as well as for immunotherapy and radioimmunotherapy) of neoplasms in mammals, preferably humans. Several mAbs or derivatives thereof (e.g., BEXXAR~~Bexxar~~®, ONCOSCINT~~OncoScint~~®, PROSTASCINT~~ProstaScint~~®, VERLUMA~~Verluma~~®, CEASCAN~~CEAScan~~®, ZEVALIN~~Zevalin~~®) have received clinical approval for radioimmunoscintigraphy or radioimmunotherapy. All these target neoplasms based on the cells of origin of the tumor (e.g., carcinoma, sarcoma., lymphoma, etc.). In contrast, the present invention targets neoplasms based on the inappropriate expression of Met and/or hHGF, which has been correlated with poor prognosis in a wide range of human solid tumors not limited by tissue of origin. In neoplastic cells the aberrant expression of Met and HGF leads to emergence of an invasive/metastatic phenotype.

[0121] Several mAbs or derivatives thereof that have received clinical approval for radioimmunoscintigraphy or radioimmunotherapy (e.g., BEXXAR~~Bexxar~~®, ONCOSCINT~~OncoScint~~®, PROSTASCINT~~ProstaScint~~®, VERLUMA~~Verluma~~®, CEASCAN~~CEAScan~~®, ~~Zevalin~~® all target neoplasms based on the tumor's cells of origin (e.g., carcinoma, sarcoma., lymphoma, etc.). In contrast, anti-hMet mAbs alone or in combination with anti-hHGF mAbs target neoplasms based on the inappropriate expression of Met and/or hHGF, which has been correlated with poor prognosis in a wide range of human solid tumors. In neoplastic cells the aberrant expression of Met and HGF leads to emergence of an invasive/metastatic phenotype. Such radiolabeled mAbs are effective at detecting Met- and/or HGF/SF-expressing tumors in humans.

[0126] Common fluorescent labels include fluorescein, rhodamine, dansyl, phycoerythrin, phycocyanin, allophycocyanin, o-phthaldehyde and fluorescamine. The fluorophore, such as the dansyl group, must be excited by light of a particular wavelength to fluoresce. See, for example,

Haugland, Handbook of Fluorescent Probes and Research Chemicals, Sixth Ed., Molecular Probes, Eugene, Oreg., 1996). Fluorescein, fluorescein derivatives and fluorescein-like molecules such as OREGON GREEN~~Oregon Green~~™ and its derivatives, RHODAMINE GREEN~~Rhodamine Green~~™ and RHODAL GREEN~~Rhodol Green~~™, are coupled to amine groups using the isothiocyanate, succinimidyl ester or dichlorotriazinyl-reactive groups. Similarly, fluorophores may also be coupled to thiols using maleimide, iodoacetamide, and aziridine-reactive groups. The long wavelength rhodamines, which are basically RHODAMINE GREEN~~Rhodamine Green~~™ derivatives with substituents on the nitrogens, are among the most photostable fluorescent labeling reagents known. Their spectra are not affected by changes in pH between 4 and 10, an important advantage over the fluoresceins for many biological applications. This group includes the tetramethylrhodamines, X-rhodamines and TEXAS RED~~Texas Red~~™ derivatives. Other preferred fluorophores for derivatizing the peptide according to this invention are those which are excited by ultraviolet light. Examples include cascade blue, coumarin derivatives, naphthalenes (of which dansyl chloride is a member), pyrenes and pyridyloxazole derivatives. Also included as labels are two related inorganic materials that have recently been described: semiconductor nanocrystals, comprising, for example, cadmium sulfate (Bruchez, M. et al., Science 281:2013-2016 (1998), and quantum dots, e.g., zinc-sulfide-capped cadmium selenide (Chan, W. C. W. et al., Science 281:2016-2018 (1998)).

[0147] The antibodies of the present invention are also useful as affinity ligands for binding to Met or to cells expressing Met in assays, preparative affinity chromatography and solid phase separation of molecules from a mixture that includes Met. Such antibody compositions may also be used to identify, enrich, purify or isolate cells to which the antibodies bind, using flow cytometric and/or solid phase methodologies. The mAb may be immobilized using conventional methods, e.g. binding to CNBr-activated SEPHAROSE~~Sepharose~~® or AGAROSE~~Agarose~~®, NHS-

AGAROSE~~Agarose~~® or SEPHAROSE~~Sepharose~~®, epoxy-activated SEPHAROSE~~Sepharose~~® or AGAROSE~~Agarose~~® EAH-SEPHAROSE~~Sepharose~~® or AGAROSE~~Agarose~~®, streptavidin-SEPHAROSE~~Sepharose~~® or AGAROSE~~Agarose~~® in conjunction with biotinylated mAb. In general the mAbs of the invention may be immobilized by any other method which is capable of immobilizing these compounds to a solid phase for the indicated purposes. See, for example Affinity Chromatography: Principles and Methods (Pharmacia LKB Biotechnology). Thus, one embodiment is a composition comprising a mAb or mixture thereof, as described herein, bound to a solid support or a resin. The compound may be bound directly or via a spacer, preferably an aliphatic chain having about 2-12 carbon atoms.

[0148] By "solid phase" or "solid support" or "carrier" is intended any support or carrier capable of binding the mAb or derivative. Well-known supports, or carriers, in addition to SEPHAROSE~~Sepharose~~® or AGAROSE~~Agarose~~® described above are glass, polystyrene, polypropylene, polyethylene, dextran, nylon, amylases, natural and modified celluloses such as nitrocellulose, polyacrylamides, polyvinylidene difluoride, other agaroses, and magnetite, including magnetic beads. The carrier can be totally insoluble or partially soluble. The support material may have any possible structural configuration so long as the coupled molecule is capable of binding to receptor material. Thus, the support configuration may be spherical, as in a bead, or cylindrical, as in the inside surface of a test tube or microplate well, or the external surface of a rod. Alternatively, the surface may be flat such as a sheet, test strip, bottom surface of a microplate well, etc.

[0235] Immunohistochemical analysis of Met expression and distribution in formalin-fixed, paraffin-embedded sections of human tissues was performed as described in Knudsen et al., supra, modified as follows: Tissue sections on microscope slides were incubated with Met3 and processed

with the VENTANA~~Ventana~~® automated system. Slides were examined by conventional light microscopy.